

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

GILES, Allen, Frank
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year) 18 September 2000 (18.09.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PHM 70442/WO	
International application No. PCT/GB99/04305	International filing date (day/month/year) 17 December 1999 (17.12.99)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address GILES, Allen, Frank AstraZeneca UK Limited Global Intellectual Property Mereside, Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom	State of Nationality	State of Residence
	Telephone No. 01625/516573	
	Facsimile No. 01625/583358	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address GILES, Allen, Frank AstraZeneca Global Intellectual Property P.O. Box 272 Mereside, Alderley Park Macclesfield, Cheshire SK10 4GR United Kingdom	State of Nationality	State of Residence
	Telephone No. 01625/516573	
	Facsimile No. 01625/583358	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Dominique DELMAS Telephone No.: (41-22) 338.83.38
--	---

09369066-002401

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

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AstraZeneca
Global Intellectual Property
P.O. Box 272
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Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

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PHM 70442/WO

IMPORTANT NOTIFICATION

International application No.

PCT/GB99/04305

International filing date (day/month/year)

17 December 1999 (17.12.99)

1. The following indications appeared on record concerning:

☒

the applicant

☐

the inventor

☐

the agent

☐

the common representative

Name and Address

ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒

the person

☒

the name

☒

the address

☒

the nationality

☒

the residence

Name and Address

ASTRAZENECA AB
S-151 85 Södertälje
Sweden

State of Nationality

SE

State of Residence

SE

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒

the receiving Office

☐

the International Searching Authority

☒

the International Preliminary Examining Authority

☐

the designated Offices concerned

☒

the elected Offices concerned

☐

other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Dominique DELMAS

Telephone No.: (41-22) 338.83.38

09869066-002401

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PHM 70442/WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 99/ 04305	International filing date (day/month/year) 17/12/1999	(Earliest) Priority Date (day/month/year) 23/12/1998
Applicant ZENECA LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

SINGLE NUCLEOTIDE POLYMORPHISM IN A PYRUVATE DEHYDROGENASE KINASE ISOENZYME 2 (PDK2) IN HUMANS

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/04305

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 7-9 (all partially), 10, 11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-9 (all partially), 10, 11

1) Claims 7 and 8 are unclear (Art. 6 PCT). In view of the complete absence of any limitation as to the length and/or the position of the nucleotide complementary to the SNP in the PDK2 gene, it is impossible for the skilled person to clearly and unambiguously understand which oligonucleotides actually fall within the scope of the said claims. Moreover, also the annealing conditions play a role: an oligonucleotide which under highly stringent conditions would not allow the detection of the allele, could be effective under less stringent conditions. Even the description adds up to the unclarity, stating that up to 10 nt can be varied with respect to the PDK2 gene sequence (p. 10, last par.). Hence, the search concerning the subject-matter of claims 7 and 8 (and therefore 9 as well) has been limited to oligonucleotides at least 8 bases long and whose last 8 nucleotides at the 3'-end correspond to one of the alleles disclosed in the present application, i.e. their 3'-end nucleotide corresponds to the nucleotide at positions 288, 1281 and 1357 of either the "wild type" sequence or the variant sequence disclosed in the application.

2) Claims 10 and 11 relate to the use of "PDK2 drugs". The description, however, does not provide any indication whatsoever as to any such drugs, it merely refers to two prior art documents. However, the two documents referred to in this context (p. 12, l. 10-12, both cited in the search report) disclose compounds which showed an in vitro inhibitory effect on PDK, but fall short of teaching an actual use of the said compounds as drugs.

Hence, since the actual meaning of the expression PDK2 drugs is completely unclear, no meaningful search with respect to the subject-matter of claims 10 and 11 is possible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

GB 99/04305

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R. GUDI ET AL.: "Diversity of the Pyruvate Kinase Gene Family in Humans" JOURNAL BIOLOGICAL CHEMISTRY, vol. 270, no. 48, 1 December 1995 (1995-12-01), pages 28989-28994, XP002135818 US cited in the application the whole document ---	1
A	ESPINAL J ET AL: "Inhibition of pyruvate dehydrogenase kinase by halogenated acetophenones" DRUG DEVELOPMENT RESEARCH, US, NEW YORK, NY, vol. 35, no. 3, 1 July 1995 (1995-07-01), pages 130-136, XP000611456 ISSN: 0272-4391 the whole document ---	4

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

20 April 2000

Date of mailing of the international search report

197.03.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Luzzatto, E

INTERNATIONAL SEARCH REPORT

International Application No

GB 99/04305

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WHITEHOUSE S. ET AL.: "Mechanism of activation of pyruvate dehydrogenase by dichloroacetate and other halogenated carboxylic acids"</p> <p>THE BIOCHEMICAL JOURNAL, vol. 141, no. 3, September 1974 (1974-09), pages 761-774, XP000886200 UK cited in the application the whole document</p> <p>-----</p>	4

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

**NOTIFICATION OF RECEIPT
OF SEARCH COPY**

(PCT Rule 25.1)

To:

Global Intellectual Property
AstraZeneca PLC
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
UNITED KINGDOM

Date of mailing
(day/month/year)

31/01/2000

Applicant's or agent's file reference

PHM 70442/WO

IMPORTANT NOTIFICATION

International application No.

PCT/GB 99/ 04305

International filing date(day/month/year)

17/12/1999

Priority date (day/month/year)

23/12/1998

Applicant

ZENECA LIMITED et al.

1. Where the International Searching Authority and the Receiving Office are not the same office:

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

Where the International Searching Authority and the Receiving Office are the same office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

14/01/2000 (date of receipt).

2. ☐ The search copy was accompanied by a nucleotide and/or amino acid sequence listing in computer readable form.

3. Time limit for establishment of International Search Report

The applicant is informed that the time limit for establishing the International Search Report is 3 months from the date of receipt indicated above or 9 months from the priority date, whichever time limit expires later

4. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the Receiving Office.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
Fax: (+31-70) 340-3016

Authorized officer

ISA/EP

INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/GB 99/04305

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 April 2000

Date of mailing of the international search report

Name and mailing address of the ISA

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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Luzzatto, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04305

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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International application No.
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because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 7-9 (all partially), 10, 11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-9 (all partially), 10, 11

1) Claims 7 and 8 are unclear (Art. 6 PCT). In view of the complete absence of any limitation as to the length and/or the position of the nucleotide complementary to the SNP in the PDK2 gene, it is impossible for the skilled person to clearly and unambiguously understand which oligonucleotides actually fall within the scope of the said claims. Moreover, also the annealing conditions play a role: an oligonucleotide which under highly stringent conditions would not allow the detection of the allele, could be effective under less stringent conditions. Even the description adds up to the unclarity, stating that up to 10 nt can be varied with respect to the PDK2 gene sequence (p. 10, last par.). Hence, the search concerning the subject-matter of claims 7 and 8 (and therefore 9 as well) has been limited to oligonucleotides at least 8 bases long and whose last 8 nucleotides at the 3'-end correspond to one of the alleles disclosed in the present application, i.e. their 3'-end nucleotide corresponds to the nucleotide at positions 288, 1281 and 1357 of either the "wild type" sequence or the variant sequence disclosed in the application.

2) Claims 10 and 11 relate to the use of "PDK2 drugs". The description, however, does not provide any indication whatsoever as to any such drugs, it merely refers to two prior art documents. However, the two documents referred to in this context (p. 12, l. 10-12, both cited in the search report) disclose compounds which showed an in vitro inhibitory effect on PDK, but fall short of teaching an actual use of the said compounds as drugs.

Hence, since the actual meaning of the expression PDK2 drugs is completely unclear, no meaningful search with respect to the subject-matter of claims 10 and 11 is possible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) PHM 70442/WO

Box No. I TITLE OF INVENTION	
CHEMICAL COMPOUNDS	
Box No. II APPLICANT	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) ZENECA Limited 15 Stanhope Gate London W1Y 6LN	
<input type="checkbox"/> This person is also inventor.	
Telephone No. +44-1625-516173	
Facsimile No. +44-1625-583358	
Teleprinter No. 669095/669388	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) ANAND, Rakesh Mereside, Alderley Park Macclesfield Cheshire SK10 4TG GB	
This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
<input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) GILES, Allen Frank Global Intellectual Property AstraZeneca PLC Mereside, Alderley Park, Macclesfield, Cheshire. SK10 4TG. GB.	
Telephone No. +44-1625-516573	
Facsimile No. +44-1625-583358	
Teleprinter No. 669095/669388	
<input type="checkbox"/> Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MORTEN, John Edward Norris
Mereside,
Alderley Park
Macclesfield
Cheshire
SK10 4TG
GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
GB

State (that is, country) of residence:
GB

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SMITH, John Craig
Mereside,
Alderley Park
Macclesfield
Cheshire
SK10 4TG
GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
GB

State (that is, country) of residence:
GB

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a)(mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

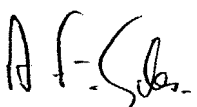
National Patent (if other kind of protection or treatment desired, specify on dotted line):

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| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> PL Poland |
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| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RO Romania |
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| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> SD Sudan |
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| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- | | | |
|--|---|---|
| <input checked="" type="checkbox"/> KR Republic of Korea | <input checked="" type="checkbox"/> DM DOMINICA | <input checked="" type="checkbox"/> ZA SOUTH AFRICA |
| <input checked="" type="checkbox"/> KZ Kazakhstan | <input checked="" type="checkbox"/> UE UNITED ARAB EMIRATES | <input checked="" type="checkbox"/> TZ TANZANIA |
| <input checked="" type="checkbox"/> LC Saint Lucia | <input checked="" type="checkbox"/> CR COSTA RICA | <input checked="" type="checkbox"/> MA MOROCCO |
| <input checked="" type="checkbox"/> LK Sri Lanka | | |
| <input checked="" type="checkbox"/> LR Liberia | | |

Precautionary Designation Statement: In addition to the designations made above the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 23DEC98 (23/12/98)	9828256.9	GB		
item (2)				
item (3)				
<input checked="" type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s) (1)				
<small>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.</small>				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) <small>(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):</small>		Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):		
ISA /		Date (day/month/year)	Number	Country (or regional Office)
Box No. VIII CHECK LIST; LANGUAGE OF FILING				
This international application contains the following number of sheets: request : 4 description (excluding sequence listing part) : 18 claims : 03 abstract : 01 drawings : - sequence listing part of description : 02 Total number of sheets : 28		This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input checked="" type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input checked="" type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input type="checkbox"/> other (specify):		
Figure of the drawings which should accompany the abstract:		Language of filing of the international application: ENGLISH		
Box No. IX SIGNATURE OF APPLICANT OR AGENT				
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).				
				
GILES, Allen Frank AGENT FOR THE APPLICANT				

For receiving Office use only	
1. Date of actual receipt of the purported international application: 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 4. Date of timely receipt of the required corrections under PCT Article 11(2): 5. International Searching Authority (if two or more are competent): ISA /	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received: 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PHM 70442/WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB99/04305	International filing date (day/month/year) 17/12/1999	Priority date (day/month/year) 23/12/1998
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant ASTRAZENECA AB et al.		


1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 08/06/2000	Date of completion of this report 08.11.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Luzzatto, E Telephone No. +49 89 2399 8169



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/04305

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-18 as originally filed

Claims, No.:

1-12 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 7-9 (PARTIALLY), 10 AND 11 (COMPLETELY).

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/04305

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 7-9 (partially), 10, 11.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9, 12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9, 12
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9, 12
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/04305

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

No search report has been established with respect of the subject-matter of claims 10 and 11 (see part VIII (1) and (3) hereinbelow).

Claims 7-9 have been searched only partially (see part V (2) and VIII (2) hereinbelow); an opinion can thus be given only with respect to the searched subject-matter.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1) No available document discloses or suggests a single nucleotide polymorphism in the PDK2 human gene at positions 288, 1281 or 1357 of the PDK2 sequence submitted to the GenBank database with accession number L42451. Hence, the subject-matter of claims 1-6 and 12 appears to meet the requirements of Art. 33 PCT (see however Part VIII hereinbelow).
- 2) Claims 7-9 have been searched only partially (see ISA Form 210).
Oligonucleotides whose 5'-end base corresponds to the mutated positions as presently claimed are neither disclosed nor suggested in any of the available documents. Therefore, the subject-matter of claims 7-9, insofar as limited to the said oligonucleotides, meets the requirements of Art. 33 PCT.

Re Item VIII

Certain observations on the international application

- 1) Claims 1-5 and 10 do not meet the requirements of Art. 6 PCT (lack of support) and their subject-matter contravenes Art. 5 PCT.
The description provides no indication whatsoever as to the actual link between the SNP at positions 288, 1281 and 1357 and a physical status, clinical response or predisposition to diseases. Indeed, no evidence is provided even as to the very existence of such a link.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/04305

- 2) Claims 7, 8 and 9 are unclear (Art. 6 PCT).

In view of the complete absence of any limitation as to the length and/or the position of the nucleotide complementary to the SNP in the PDK2 gene, it is impossible for the skilled person to clearly and unambiguously understand which oligonucleotides actually fall within the scope of the said claims. Moreover, also the annealing conditions play a role: an oligonucleotide which under highly stringent conditions would not allow the detection of the allele, could be effective under less stringent conditions. Even the description adds up to the unclarity, stating that up to 10 nt can be varied with respect to the PDK2 gene sequence. Hence, these claims should have been deleted.

- 3) No "PDK2 drugs" are disclosed in the application. The documents referred to with respect to this issue (P. 12, L. 10-12) only discloses putative PDH inhibitors. Hence, the skilled person has no indication whatsoever as to any such drug and, thus, as to any possible use thereof in combination with the disclosed SNP. Claims 10 and 11, therefore, contravene Art. 6 PCT due to lack of clarity.

- 4) The expression "antisense sequence thereto" in claim 6 is unclear and should thus have been deleted.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PHM 70442/WO	<div style="display: flex; justify-content: space-between;"> <div>FOR FURTHER ACTION</div> <div>See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)</div> </div>	
International application No. PCT/GB99/04305	International filing date (<i>day/month/year</i>) 17/12/1999	Priority date (<i>day/month/year</i>) 23/12/1998
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant ASTRAZENECA AB et al.		

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- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 08/06/2000	Date of completion of this report 08.11.2000
Name and mailing address of the international preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 </div> </div>	Authorized officer Luzzatto, E Telephone No. +49 89 2399 8169



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/04305

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

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Claims, No.:

1-12 as originally filed

2. The amendments have resulted in the cancellation of:

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☐ the claims, Nos.:
☐ the drawings, sheets:

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4. Additional observations, if necessary:

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☒ claims Nos. 7-9 (PARTIALLY), 10 AND 11 (COMPLETELY).

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/04305

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 7-9 (partially), 10, 11.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-9, 12
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-9, 12
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-9, 12
	No:	Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/04305

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Certain observations on the international application

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/04305

2) Claims 7, 8 and 9 are unclear (Art. 6 PCT).

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